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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/464,416	12/16/99	THANAVALA Y	RPP:156BUS

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1651	9

DATE MAILED: 10/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/464,416	Thanavala et al.
Examiner	**Group Art Unit**
Michele Flood	1651

☒ Responsive to communication(s) filed on *Jul 20, 2000* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-3 and 5-12* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3 and 5-12* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4 & 6

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on July 20, 2000. Acknowledgment is made of Applicant's cancellation of Claim 4, and the claim was withdrawn from further consideration by the Examiner under 37 CFR 1.142 (b).

The rejection made under 35 U.S.C. 112 has been overcome by Applicant's amendment of the claims.

The rejection of Claims 1, 3 and 5-12 made 35 U.S.C. 103(a) as being unpatentable over Koprowski et al. in view of Stites et al. has been overcome by Applicant's amendment of the claims.

The rejection of Claims 1-2 and 4-12 made under 35 U.S.C. 103(a) as being unpatentable over Arntzen et al. in view of Koprowski et al., and further in view of Stites et al. has been overcome by Applicant's cancellation of Claim 4.

Claims 1-3 and 5-12 are under examination.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-3 and 5-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-3 and 5-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method of providing an response in a mammal to the non-enteric pathogen antigen (NAPA), hepatitis B surface antigen (HBsAg), which is induced by the oral administration of genetically altered plant material of the family *Solanaceae* expressing the HBsAg in combination with an orally effective adjuvant, does not reasonably provide enablement for providing an immune response to a non-enteric pathogen selected from the group consisting of pathogens which cause the infectious diseases hepatitis C, hepatitis delta, yellow fever, dengue, hemorrhagic fever, tetanus, *Staphylococcus aureries*, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever.

The claims are drawn to a method for providing an response in a mammal and/or a human comprising the oral administration of a substance comprising physiologically acceptable genetically altered plant material of the *Solanaceae* which expresses a NEPA, wherein the NEPA is an antigen specific to a non-enteric pathogen selected from the group consisting of those pathogens which cause the infectious diseases hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue, hemorrhagic fever, tetanus, *Staphylococcus aureus*, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever, in combination with an orally effective adjuvant.

The specification broadly discloses non-enteric pathogens that invade the epidermis of mammals via punctures, abrasions, cuts or other breaches in the skin, e.g. blood transfusions

which can be used as sources of NEPA to raise a protective enteric immune response in mammals. However, the specification does not provide sufficient guidance as to how one of ordinary skill in the art would provide an immune response in a mammal and/or a human to a NEPA other than the non-enteric pathogen antigen, hepatitis B surface antigen. The specification does not disclose other specific non-enteric pathogen antigens which have been subjected to the claim-designated therapeutic regimen, nor does the specification teach any methodology associated with the making of genetically altered plant materials expressing any other NEPA other than the non-enteric pathogen antigen, hepatitis B surface antigen. In regard to Claim 3, the specification other than the mere suggestion on page 1, lines 13-16 does not provide guidance as to how to use the instantly claimed invention to provide an immune response to any all diseases caused by a non-enteric pathogen that invade the epidermis of mammals via punctures, abrasions, cuts or other breaches in the skin. Moreover, there is inadequate guidance as to how one of ordinary skill in the art would use the instantly claimed invention to genetically altered plant material to express any and all non-enteric pathogens other than HBsAg.

Inventions targeted for human therapy bear a heavy responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatment. The standard of enablement is higher for such inventions because effective treatments for providing immunological responses to the instantly disclosed pathogens are relatively rare, and may be unbelievable in the absence of supporting evidence. Claims drawn to compositions intended for the administration of compounds to humans generally require supporting evidence which clearly

define the ingredients or constituents contained therein because of the unpredictability in biological responses to therapeutic treatments. In order to enable the skilled artisan to practice the invention as claimed, applicant would have to demonstrate the functional effect and describe the effective amounts of each ingredient for the administration of the composition intended for a therapeutic treatment. Accordingly, it would take undue experimentation without a reasonable expectation of success to determine which amounts of the instantly claimed plant materials expressing a non-enteric pathogen selected from those pathogens which cause the diseases hepatitis C, hepatitis delta, yellow fever, dengue, hemorrhagic fever, tetanus, *Staphylococcus aureus*, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever, and other ingredients, i.e. adjuvant, therein which would have the claimed functional effect for providing a an immune response in a mammal, wherein the specific immune response to the NEPA was stronger than a response specific to NEPA caused by the NEPA alone.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 5-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arntzen et al. (B) in view of Koprowski et al. (A), and further in view of Stites et al. (U).

The claims are directed to a method for providing an immune response in a mammal and/or human that is specific to a non-enteric pathogen antigen (NEPA), the pathogen being a pathogen that invades through a breach in the skin and that does not raise a protective enteric immune response in mammals of acquired immunity to the pathogen in the absence of an oral adjuvant, the method comprising feeding the mammal with genetically altered plant material expressing a NEPA in combination with an adjuvant, the combination causing an immune response specific which is stronger than a response caused by the oral administration of the NEPA alone. The claims are further directed to a method wherein the NEPA is an antigen specific to a non-enteric pathogen selected from the group consisting of those that cause hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue, hemorrhagic fever, tetanus, *Staphylococcus aureus*, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever. The claims are further directed to a therapeutic regimen thereof, comprising feeding the mammal/and or human a genetically altered potato from the family *Solanaceae*.

Arntzen clearly teaches an anti-viral vaccine produced in physiologically acceptable plants, particularly the potato and the tomato, and then administered through standard vaccine procedure or by feeding the plants to a mammal or a human. Arntzen specifically teaches methods of making a transgenic plant expressing an immunogen derived from hepatitis B surface antigen, wherein the immunogen is capable of eliciting an immune response in an animal by consumption of the plant material. Arntzen also teaches methods of making a vaccine by recovering the immunogen expressed in the plant cell for use as a vaccine. Moreover, Arntzen teaches that the physiologically acceptable plant materials expressing the HBsAg can be used both to prime the mucosal immune system and/or stimulate the humoral immune response in a dose dependent manner. See Column 3, lines 24, Columns 4-7 and Column 8, lines 1-21. In Column 11, lines 36-50, Arntzen teaches that either the parenteral or non-parenteral introduction of the taught vaccine to a mammal can elicit serum and/or secretory antibodies against the HBsAg immunogen of the vaccine with minimal induction of systemic tolerance. Arntzen teaches a method for providing a specific immune response in a mammal to the non-enteric pathogen antigen, hepatitis B surface antigen by feeding a mammal with genetically altered physiologically acceptable plant material of a potato which is of the family *Solanaceae*. Arntzen does not teach a method for providing a specific immune response by feeding a mammal with genetically altered potato expressing a NEPA with an adjuvant, wherein the drug combination causes an immune response which is stronger than a response caused by the NEPA alone. However, it would have been obvious to one of ordinary skill in the art to combine the drug taught by Arntzen with an

adjuvant because Koprowski teaches a method of making microbially transinfected plants expressing a viral antigen which can be used as an oral delivery system to elicit an immunologic response in a mammal, including a human. Solanaceous plants can be used as a source of physiologically acceptable material. See Column 8, lines 24-31. Koprowski also teaches that when the plant material containing the NEPA is delivered, it can be delivered with an adjuvant to facilitate or improve its immunological therapeutic activity. See Column 6, lines 22-36. One of ordinary skill in the art would have been motivated with a reasonable expectation of success that the oral delivery to a mammal, including a human, the drug taught by Arntzen with the adjuvant taught by Koprowski would induce an immune response in a mammal to the specific non-enteric pathogen, HBsAg, wherein the specific immune response was a an immune response which was stronger that a response specific to a NEPA caused by the NEPA alone due to the oral administration of genetically altered potato plant material in combination with an adjuvant because, at the time the invention was made, it was well known in the art as taught by Stites that adjuvants enhance the response of an immunogen, such as a NEPA, when the adjuvant is administered in combination with the immunogen. See page 102. Thus, the results are no more than the mere combination of known drugs administered by very old an well known methods in the art because Arntzen, as well as Stites, teach that protective immunity can be effected by the multiple administration of a vaccine over a period of time. For example, the art of immunology recognizes the routine practice of inducing immunity, acquired immunity or actively acquired immunity which is demonstrated by an antibody response that may or may not relate to specific immunity to

infection or disease by vaccination or artificial immunization to provide or elicit an immune response. Thus, one of ordinary skill in the art would have had a reasonable expectation of success that feeding an individual with an oral vaccine comprising genetically altered potato from the family *Solanaceae* containing HBsAg which further comprises an adjuvant would provide a stronger specific response to the NEPA than caused by the NEPA alone. Finally, one of ordinary skill in the art at the time the invention was made would have been motivated to optimize the teachings of Arntzen by providing an immune response in an individual, comprising a therapeutic regimen of ingesting the plant material in a plurality of different times and dose ranges because Arntzen teaches that a plurality of different administrations of the genetically altered plant material expressing HBsAg over separate periods of time will achieve immunization. Note that Arntzen specifically teaches that the plurality of times for the administration of the vaccines is in a range of 3 to 6, and that the time separating the vaccinations is in a range of 14 to 35 days to achieve protective levels of antibodies. See Column 15, lines 45-61. Stites also teaches that the timing of primary immunization, the interval doses, and the timing of reimmunization administrations are based on both theoretic considerations and vaccine administrations. Thus, one would have had a reasonable level of providing a therapeutic regimen such as the one in the claimed invention because the determination of an effective treatment method for providing an immune response by the oral ingestion of the claim-designated drug in combination with an adjuvant in an individual which was greater than the response elicited by the NEPA alone would have been a matter of routine optimization to one of ordinary skill in the art at the time the invention was made.

Accordingly, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

No claims are allowed.

Conclusion

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is (703) 308-9432. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196 or the Supervisory Patent Examiner, Michael Wityshyn whose telephone number is (703) 308-4743.

LEON B. LANKFORD, JR.
PRIMARY EXAMINER

mcf

September 25, 2000